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A further study of the synthesis of 5,5-Alkylphenylbarbituric acids

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A FURTHER STUDY OF THE SYNTHESIS OF 5, 5-ALKYLPHENYLBARBITURIC ACIDS

TAYLOR 1935

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OF

5,5-ALKYLPHENYLBARBITURIC ACIDS

by

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INTRODUCTION

Alkylphenylbarbituric acids, which may also be called alkylphenylmalonylureas, have the following constitution:

```
           CO - HN
  R \      |4    3|
     \_____C5    2C = O
     /
  R /      |6    1|
           CO - HN
```

In Veronal, one of the first barbituric acids to be used as a drug, R and R are both ethyl radicals. Luminal, also called Phenobarbital, is the ethylphenylbarbituric acid. The syntheses of this latter compound, the ethylphenylbarbituric acid and also of the isoamyl and the heptylphenylbarbituric acids were studied in this laboratory by James J. Chap.[1] Isopropylphenylbarbituric acid was studied here by James E. Doyle,[2] and hexylphenylbarbituric acid by L. Bayard Spaulding.[3] All of this work was based on the syntheses of Rising and Stieglitz,[4] Rising and Zee,[5,6] and Nelson and Cretcher[7] as discussed in the theses referred to.

In the present investigation emphasis has been placed on the type reactions common to syntheses of all of the barbituric acids prepared, rather than on the individual reactions pertaining to each particular barbituric acid. However, in order to compare the syntheses worked out previously, as found in the literature, the reaction for each step in the preparation of the final barbituric acid from the beginning compound will be given.

In 1918 Rising and Stieglitz[4] prepared ethylphenylbarbituric acid by the so-called "war-time" synthesis, summarized by the following reactions:

I. $C_6H_5CH_2CN + CH_3OH + HCl \dashrightarrow C_6H_5CH_2CO_2CH_3 + NH_4Cl$

Phenylacetonitrile — Methyl phenylacetate

II. $C_6H_5CH_2CO_2CH_3 + (CO_2CH_3)_2 + NaOC_2H_5 \dashrightarrow CH_3O_2C\text{-}C(ONa)=C(C_6H_5)CO_2CH_3 + C_2H_5OH$

Methyl phenylacetate — Di methyl oxalate — Dimethyl oxalylphenylacetate sodium salt

III. $CH_3O_2C\text{-}C(ONa)=C(C_6H_5)CO_2CH_3 + H_2SO_4 \dashrightarrow CH_3O_2C\text{-}CO\text{-}CH(C_6H_5)CO_2CH_3 + NaHSO_4$

Dimethyl oxalylphenylacetate sodium salt — Dimethyl oxalylphenylacetate

IV. $CH_3O_2C\text{-}CO\text{-}CH(C_6H_5)CO_2CH_3 \dashrightarrow (C_6H_5)CH(CO_2CH_3)_2 + CO$

Dimethyl oxalylphenylacetate — Dimethyl phenylmalonate

V. $(C_6H_5)CH(CO_2CH_3)_2 + NaOCH_3 + C_2H_5I \dashrightarrow (C_6H_5)(C_2H_5)C(CO_2CH_3)_2 + NaI + CH_3OH$

Dimethyl phenylmalonate — Dimethyl ethylphenylmalonate

VI. $(C_6H_5)(C_2H_5)C(CO_2CH_3)_2 + CO(NH_2)_2 \dashrightarrow (C_6H_5)(C_2H_5)C - CONHCONHCO$

Dimethyl ethylphenylmalonate — Urea — 5,5-Ethylphenylbarbituric acid

In attempting to increase the yield of dimethyl ethylphenylmalonate, in 1927, Rising and Zee[5] developed a new synthesis according to the following reactions:

I. $C_6H_5CH_2CN + NH_2Na + C_2H_5I \dashrightarrow (C_6H_5)CH(C_2H_5)(CN) + NaI + NH_3$

Phenylacetonitrile — Sodamide — Ethylphenylacetonitrile

II. $2C_6H_5CH(C_2H_5)(CN) + 2Na \dashrightarrow 2C_6H_5CNa(C_2H_5)(CN) + H_2$

Ethylphenylacetonitrile — Ethylphenylacetonitrile sodium salt

III. $C_6H_5CNa(C_2H_5)(CN) + ClCO_2CH_3 \dashrightarrow C_6H_5C(CO_2CH_3)(C_2H_5)(CN) + NaCl$

Ethylphenylacetonitrile, sodium salt — Methyl chloroformate — Methyl cyanoethylphenyl acetate

IV. $C_6H_5C(CO_2CH_3)(C_2H_5)(CN) + CH_3OH + HCl \dashrightarrow C_6H_5C(CO_2CH_3)(C_2H_5)C(:NH_2Cl(OCH_3)$

Methyl cyanoethylphenylacetate — Methyl ethylphenylmalonate methyl iminoester hydrochloride

V. $C_6H_5C(CO_2CH_3)(C_2H_5)C(:NH_2Cl)(OCH_3) + HOH \dashrightarrow C_6H_5C(C_2H_5)(CO_2CH_3)_2 + NH_4Cl$
Methyl ethylphenylmalonate methyl iminoester hydrochloride — Dimethyl ethylphenylmalonate

VI. $C_6H_5C(C_2H_5)(CO_2CH_3)_2 + OC(NH_2)_2 \dashrightarrow (C_6H_5)(C_2H_5\overline{C\text{-}CONHCONH - C}O$
Dimethyl ethylphenylmalonate — 5,5-Ethylphenylbarbituric acid

Although Rising and Zee obtained the desired ester by this synthesis, the yield was not increased. In the following year they improved the method[6] by introducing the methyl group into the ethylphenylacetonitrile and by reacting the sodium salt of methylethylphenylmalonate with methyl chloroformate.

I. $(C_6H_5)CH_2(CN) + NaNH_2 + C_2H_5I \dashrightarrow (C_6H_5)(C_2H_5)CH(CN) + NaI + NH_3$
Phenylacetonitrile — Sodamide — Ethylphenylacetonitrile

II. $(C_6H_5)(C_2H_5)CH(CN) + CH_3OH + HCl \dashrightarrow (C_6H_5)C_2H_5)CHC(=NH_2Cl)(OCH_3)$
Ethylphenylacetonitrile — Ethylphenylacetic methyl iminoester hydrochloride

III. $(C_6H_5)(C_2H_5)CHC(=NH_2Cl)(OCH_3) + H_2O \dashrightarrow (C_6H_5)(C_2H_5)CH(CO_2CH_3) + NH_4Cl$
Ethylphenylacetic methyl iminoester hydrochloride — Methyl ethylphenylacetate

IV. $2(C_6H_5)(C_2H_5)CH(CO_2CH_3) + 2Na \dashrightarrow 2(C_6H_5)(C_2H_5)C{=}C(OCH_3)(ONa) + H_2 \uparrow$
Methyl ethylphenylacetate — Methyl ethylphenylacetate Sodium salt

V. $(C_6H_5)(C_2H_5)C = C(OCH_3)(ONa) \dashrightarrow (C_6H_5)(C_2H_5)C(CO_2CH_3)Na$
Enol form — Keto form

VI. $(C_6H_5(C_2H_5)C(CO_2CH_3)Na + ClCO_2CH_3 \dashrightarrow (C_6H_5)(C_2H_5)C(CO_2CH_3)_2 + NaCl$
Sodium salt — Methyl chloroformate — Dimethyl ethylphenylmalonate

VII. $(C_6H_5)(C_2H_5)C(CO_2CH_3)_2 + OC(NH_2) \dashrightarrow (C_6H_5)(C_2H_5)\overline{C\text{-}CONHCONH\text{-}C}O$
Dimethyl ethylphenylmalonate — Urea — 5,5-Ethylphenylbarbituric acid

Nelson and Cretcher[7] simplified the preparation of diethyl ethylphenylmalonate as shown by the following reactions:

I. $C_6H_5CH_2CN + OC(OC_2H_5)_2 + NaNH_2 \longrightarrow (CN)(C_6H_5)CH\text{-}CO_2C_2H_5 + NH_3 + NaOC_2H_5$
Phenylaceto-nitrile, Diethyl carbonate, Sodamide, Ethyl cyanophenyl-acetate

II. $(CN)(C_6H_5)CHCO_2C_2H_5 + HCl + C_2H_5OH \xrightarrow{HOH} C_6H_5CH(CO_2C_2H_5)_2 + NH_4Cl$
Ethyl cyanophenyl acetate, Diethyl phenyl malonate

III. $C_6H_5CH(CO_2C_2H_5)_2 + C_2H_5I + C_2H_5OH \longrightarrow (C_6H_5(C_2H_5)C(CO_2C_2H_5)_2 + HI + C_2H_5OH$
Diethyl phenyl-malonate, Diethyl ethylphenyl-malonate

IV. $(C_6H_5)(C_2H_5)C(CO_2C_2H_5)_2 + OC(NH_2)_2 \longrightarrow (C_6H_5)(C_2H_5)\overline{CCONHCONHCO}$
Diethyl ethylphenyl malonate, Urea, 5,5-Ethylphenylbarbituric acid

Chap[1] further developed the technique and obtained higher yields. His synthesis of ethylphenylbarbituric acid may be summarized by these reactions.

I. $C_6H_5CH_2CN + OC(OC_2H_5)_2 + NaNH_2 \longrightarrow (C_6H_5)(CN)CH(CO_2C_2H_5) + NH_3 + C_2H_5ONa$
Phenylaceto-nitrile, Diethyl carbonate, Sodamide, Ethyl cyanophenylacetate

II. $(C_6H_5)CN)CH(CO_2C_2H_5) + C_2H_5I + C_2H_5ONa \longrightarrow (C_6H_5(C_2H_5)C(CN)(CO_2C_2H_5) + NaI + C_2H_5OH$
Ethyl cyanophenyl-acetate, Ethyl cyanoethylphenylacetate

III. $(C_6H_5)(C_2H_5)C(CN)(CO_2C_2H_5) + OC(NH_2)_2 + Na \longrightarrow (C_6H_5)C_2H_5)\overline{CCONHCONHC} = NH$
Ethyl cyanoethylphenylacetate, Urea, Ethylphenyliminobarbituric acid

IV. $(C_6H_5)(C_2H_5)\overline{CCONHCONHC} = NH + H_2O \longrightarrow (C_6H_5)(C_2H_5)\overline{CCONHCONHCO}$
Ethylphenyliminobarbituric acid, 5,5-Ethylphenylbarbituric acid

Inasmuch as the present investigation consists of a study of the three principal reactions; (a) diethyl carbonate condensation, (b) alkylation and (c) urea condensation; the syntheses priviously referred to were not carried out here. However, a brief comparison of the methods will be given.

In all of these syntheses the starting compound was phenylacetonitrile, with the objective of obtaining dialkyl ethylphenylmalonate, for once this compound had been obtained it was simply condensed with urea to form the alkylphenylbarbituric acid.

In the "war-time" synthesis phenylacetonitrile was hydrolyzed and then condensed with dimethyl oxalate. By this method two carboxyl groups were introduced, yielding finally phenylmalonic ester which was then alkylated to obtain dimethyl ethylphenylmalonate.

Rising and Zee reversed the process, first alkylating phenylacetonitrile and then introducing the two carboxyl groups, the first by methyl chloroformate, the second indirectly by the action of methyl alcohol and hydrochloric acid and the hydrolysis of the intermediate iminoacid ester.

Rising and Zee improved their technique by changing the order in which they added their reactants. As before, they alkylated phenylacetonitrile. Then they introduced the first carboxyl group by the action of methyl alcohol and hydrochloric acid and hydrolyzing the iminoacid. After one carboxyl group was already present in the molecule, the second one was introduced by means of methyl chloroformate.

Nelson and Cretcher used sodamide as a condensing agent. They condensed phenylacetonitrile with diethyl carbonate to obtain ethyl cyanophenylacetate. By treatment of this ester with ethyl alcohol and hydrochloric acid, they obtained diethyl phenylmalonate. Finally the diethyl phenylmalonate was alkylated with ethyl iodide to give diethyl ethylphenylmalonate.

In Chap's modification of Nelson and Cretcher's method the diethyl ethylphenylmalonate was not synthesized. He condensed phenylacetonitrile with diethyl carbonate and by alkylating the resulting product, obtained ethyl cyanoethylphenylacetate. This alkylated ester which contained only one carboxyl group was condensed with urea. The result was the iminobarbituric acid which upon boiling in dilute hydrochloric acid was hydrolyzed to the barbituric acid.

PLAN OF PRESENT INVESTIGATION

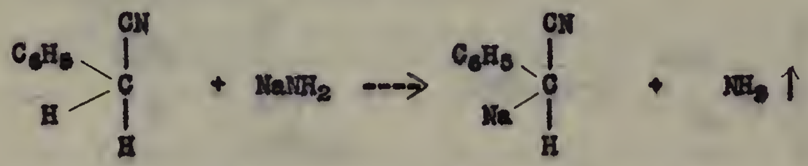
In the work of Chap and others in this laboratory there were encountered various technical difficulties, some of which require further study. These points of technique are really the substance of the study here recorded and are included under three heads as follows:

I. The diethyl carbonate condensation.

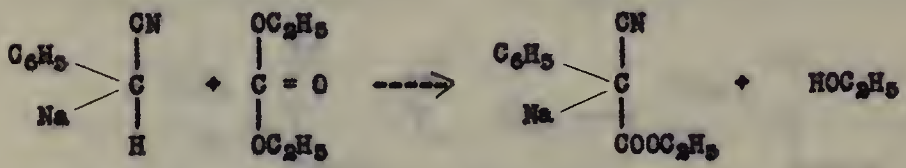
II. The alkylation.

III. The urea condensation.

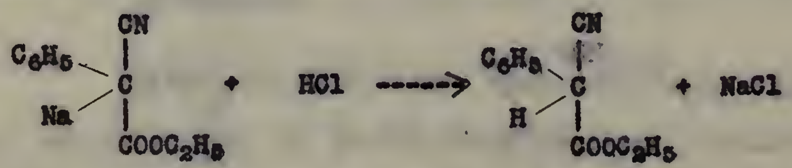
I. Diethyl carbonate condensation.



Phenylaceto-nitrile — Sodamide — Phenylacetonitrile, sodium salt



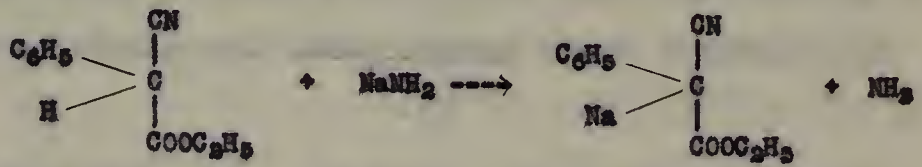
Phenylaceconitrile sodium salt — Diethyl carbonate — Ethyl cyanophenylacetate, sodium salt



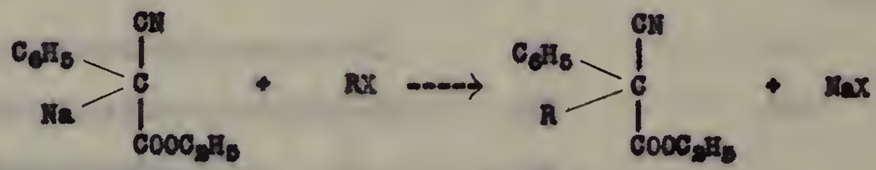
Ethyl cyanophenylacetate, sodium salt — Ethyl cyanophenylacetate

In this condensation, mentioned in the work of Nelsen and Cretcher and of Chap, the phenylacetonitrile is condensed with diethyl carbonate in order to produce the ethyl ester of cyanophenylacetic acid. Sodamide is the most efficient condensing agent so far suggested. The use of absolutely anhydrous ether (the refluxing medium), mechanical stirring, thorough refluxing and also the slow introduction of reactants, through a separatory funnel, as emphasized by Chap, were all found to be essential points of technique. The technique as developed seemed satisfactory. The maximum yield was 30%.

II. Alkylation.



Ethyl cyanophenyl-acetate | Sodamide | Ethyl cyanophenylacetate, Sodium salt



Ethyl cyanophenyl-acetate, sodium salt | Alkyl halide | Ethyl alkylcyanophenylacetate

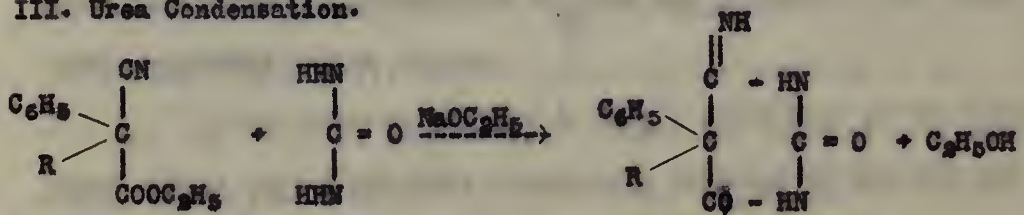
In this reaction, ethyl cyanophenylacetate is alkylated with the desired halide, RX, in the above reaction. Sodamide is used to produce the sodium salt, the sodium of which is replaced by the alkyl radical. As a part of this work, an alkylation with tertiary amyl iodide, usually considered a difficult alkylation, was effected, as later discussed on page 17.

Upon further consideration of the diethyl carbonate condensation and the alkylation reaction it was observed that the sodium salt of ethyl cyanophenylacetate is formed in both instances. In the condensation with diethyl carbonate this sodium salt which is produced is treated with hydrochloric acid, and the ethyl cyanophenylacetate is obtained by distillation under reduced pressure. In order to alkylate, the ethyl cyanophenylacetate is changed back again by sodamide to the sodium salt followed by treatment with the alkyl halide. The possibility of alkylating the sodium salt as it is formed in the diethyl carbonate condensation, that is, without isolating the free ethyl ester and subsequently reconverting it into the sodium salt, was investigated. Negative results were obtained. According to molecular weight determinations, no alkylation was effected with either isopropyl bromide or tertiary amyl iodide.

	Molecular Weight	
	Calculated	Found (freezing point method)
Ethyl cyanoisopropylphenylacetate,	231	190
Ethyl cyanotertiaryamylphenylacetate,	259	190
Ethyl cyanophenylacetate,	189	

This shows that no alkylation resulted as the product was unchanged ethyl cyanophenylacetate.

III. Urea Condensation.



Ethyl alkylcyanophenylacetate   Urea   Alkylphenyl-iminobarbituric acid

In this reaction the ethyl alkylcyanophenylacetate condenses with urea in sodium alcoholate solution to form 5,5-alkylphenyl-4-imino-barbituric acid which upon hydrolysis yields the 5,5-alkylphenylbarbituric acid. Since the yield in this step was very low, several variations were made in the procedure. According to Chap, the ethylalkylcyanophenyl-acetate, immediately followed by the urea is added to the sodium ethylate.

It was thought that by refluxing the ethyl alkylcyanophenyl-acetate with sodium ethylate the sodium salt would be formed which might condense more fully with the urea than the ethyl ester itself had. Results did not bear out this idea.

Instead of adding the urea as a dry powder, an alcoholic solution of the ethyl ester and the urea was added to the sodium alcoholate. No iminobarbituric acid was obtained.

To give the urea a good chance to condense with the ester the period of refluxing was increased from ten hours to two days and a night. Continued refluxing did not produce any iminobarbituric acid. As in the other cases only a turbidity resulted where there should have been a flocculent precipitate.

Since considerable ammonia was given off during refluxing, it was thought that a large part of the urea might be decomposing instead of condensing with the ester. Hence, an experiment was carried out in which after the usual quantities of ester and urea had refluxed for a short time a second equal quantity of urea was added. Thus, slightly more than twice the theoretical of urea was present. This excess of urea apparently had no effect.

In the case of the heptyl ester, about half of the ester was added to the sodium ethylate immediately followed by the urea and the remaining portion of ester.

This procedure resulted in a reasonable yield of the imino-barbituric acid in the case of this particular ester.

EXPERIMENTAL WORK

As previously stated, thorough stirring and refluxing and the slow introduction of the reactants are essential points of technique. To have these conditions, the apparatus consists of a three-necked balloon flask, the middle neck of which is fitted with a mercury-sealed stirrer, one side neck with a reflux condenser, and the other side neck with a separatory funnel which is often later replaced by a thermometer.

The experimental part of this work consists of the study of:

(A) The preparations of the following compounds:

I. Phenylacetonitrile.

II. Ethyl cyanophenylacetate.

Heptylphenylbarbituric acid series.

III. Ethyl cyanoheptylphenylacetate.

IV. 5,5-Heptylphenyl-4-iminobarbituric acid.

V. 5,5-Heptylphenylbarbituric acid.

Isopropylphenylbarbituric acid series.

VI. Ethyl cyanoisopropylphenylacetate.

VII. 5,5-Isopropylphenyl-4-iminobarbituric acid

VIII. 5,5-Isopropylphenylbarbituric acid (not obtained)

Tertiaryamylphenylbarbituric acid series.

IX. Ethyl cyanotertiaryamylphenylacetate.

X. 5,5-Tertiaryamylphenyl -4-iminobarbituric acid.

XI. 5,5-Tertiaryamylphenylbarbituric acid (not obtained).

(B) The modification of procedure in these preparations as discussed under "Plan of Work" and given in detail in the following pages.

Phenylacetonitrile

Phenylacetonitrile was prepared by the procedure of Roger Adams as given in "Organic Syntheses".[8]

$C_6H_5CH_2Cl$	+ $NaCN$	----→	$C_6H_5CH_2CN + NaCl$
Benzyl chloride	Sodium cyanide		Phenylacetonitrile (Benzyl cyanide)

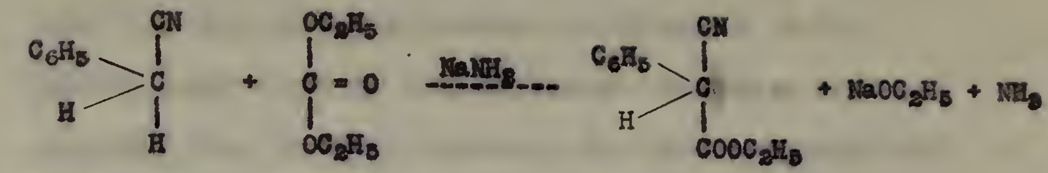
Benzyl chloride,	500 g.
Sodium cyanide,	250
Water,	225
Ethyl alcohol,	500

Two hundred fifty grams of powdered sodium cyanide were put into a flask and 225 cc. of distilled water were added. The mixture was heated to about 80° on the steam bath for two hours, at the end of which time some of the sodium cyanide still remained undissolved. The benzyl chloride and ethyl alcohol were mixed together, and the resulting solution was added dropwise, the addition being accomplished in about two hours. The temperature ranged from 40° at the beginning to 80° at the end, after the steam was turned on. During the addition of the benzyl chloride-alcohol mixture, sodium

chloride began to separate out. The temperature remained at about 82° for six hours. The reaction mixture was first a light yellow but gradually became darker, being dark brown at the end of three or four hours. The sodium chloride was filtered off with suction, and the alcohol from the filtrate was distilled off under reduced pressure, using instead of the usual reduced pressure apparatus, a balloon flask, a condenser, and for the receiving flask, a suction flask. By distilling off the alcohol under reduced pressure, the "messy" brine bath and the bumping were alleviated. The liquid remaining after the alcohol had been distilled off was distilled under reduced pressure, using the customary apparatus. The phenylacetonitrile, a clear colorless liquid, came over at 110° at 13 mm. pressure. The maximum yield was 39%.

Following the outline presented in "Plan of Present Investigation" the remainder of the experimental work will be considered from the standpoint of the three type reactions; condensation of phenylacetonitrile with diethyl carbonate, alkylation of ethyl cyanophenylacetate, and condensation of the alkylated ester with urea, as they were applied in the preparation of isopropyl-, tertiaryamyl-, and heptylphenylbarbituric acids.

I. Diethyl Carbonate Condensation.



Phenylaceto-nitrile   Diethyl carbonate   Ethyl cyanophenyl acetate

Since the alkylated esters are merely substitution products of ethyl cyanophenylacetate, the reaction given above is necessarily the same for all instances.

Phenylacetonitrile,	117 g.
Diethyl carbonate,	150
Sodamide,	42
Ester, anhydrous,	300

Forty-two grams of pulverized sodamide were added to 300 g. of anhydrous ether. One hundred seventeen grams of phenylacetonitrile were added dropwise during constant stirring. Although no heat was applied, the reaction mixture became slightly warm and ammonia was given off. An orange-yellow color gradually appeared. A medium fine precipitate (the sodium salt of phenylacetonitrile) was formed as the phenylacetonitrile dropped in. When all of the nitrile had been added, the mixture was refluxed for half an hour. By this time, the color had changed from an orange yellow to a light brown.

After cooling to room temperature, 150 g. of freshly distilled diethyl carbonate were added dropwise. When all of the carbonate had been added, the reaction mixture was refluxed for two hours. To the cold mixture, composed of a dark colored liquid and a lighter colored solid, was added dilute hydrochloric acid (1 : 9) until the solid, the

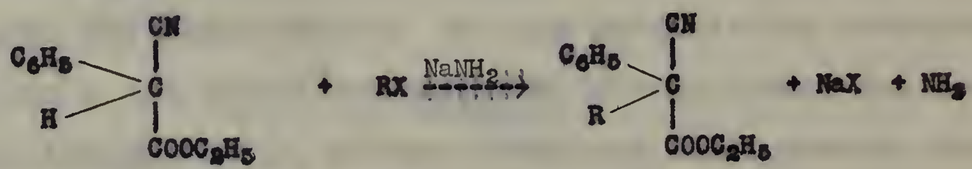
sodium salt of ethyl cyanophenylacetate, had been converted into the ethyl cyanophenylacetate and dissolved in the aqueous layer which was acid to litmus. The ether layer was separated from the water layer and the latter extracted with ether. The ether extractions were combined and dried over calcium chloride. After the ether had been distilled from the dark red solution, the remaining liquid was distilled at 13 mm. pressure. The redistilled ethyl cyanophenylacetate was a light yellow liquid coming over at 145°-165°.

Ethyl Cyanophenylacetate

	yield	b.p.	press. in mm.
Crude,	82 g. - 30%	135-170°	13
Redistilled	57 g.	145-165°	13

II. Alkylation of Ethyl Cyanophenylacetate.

The alkylation of the ethyl cyanophenylacetate was carried out according to the method of Bodroux and Taboury,[9] modified by Chap[1].



Ethyl cyanophenylacetate   Alkyl halide   Ethyl alkylcyanophenylacetate

Reactants in grams

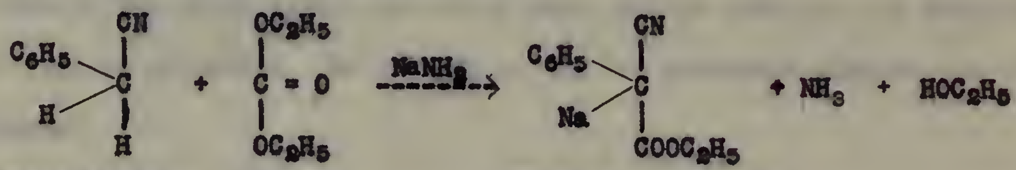
Alkylating agent	Ethyl cyanophenyl-acetate	Alkyl Halide	Sodamide	Ether anhyd.
Isopropyl bromide,	50	33	10	200
Tertiaryamyl iodide,	47.3	49.5	9.8	200
n-Heptyl bromide,	36	34	7.6	100

The powdered sodamide was added to the anhydrous ether, and then the ethyl cyanophenylacetate was introduced dropwise. Ammonia was given off and after refluxing for about six hours, a tan precipitate, the sodium salt of ethyl cyanophenylacetate, had formed. About 50 g. of absolute alcohol were then added to use up any unchanged sodamide. The alkyl halide was added drop by drop while refluxing and stirring were continued. After the halide was added the reaction mixture was refluxed for four days, the stirrer and the steam bath being turned off at night. After the excess ether had been distilled off the reaction mixture was further refluxed for eight hours. Water was then added to dissolve the sodium halide, and the aqueous layer was acidified with dilute sulphuric acid (20% by weight). The ether layer was separated and dried over calcium chloride. The ether solution of the tertiaryanyl ester was so dark colored (probably due to liberated iodine) that it was thought advisable to wash the ether extract with dilute potassium hydroxide. The resulting solution was several shades lighter when the calcium chloride was added to remove the water. By distillation under reduced pressure, the alkylated ester was obtained as a light yellow liquid.

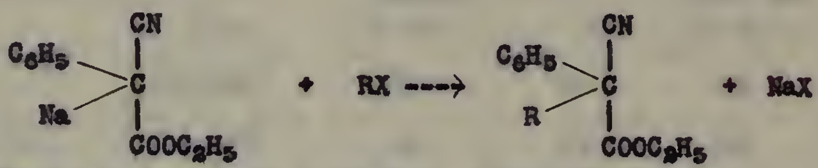
$(CN)(R)(C_6H_5)C(CO_2C_2H_5)$	b.p.	mm. press.	yield in g.	yield %
Isopropyl,	160-165°	25	25	42
Tertiaryamyl,	130-165°	10	18.5	29
n-Heptyl,	185-195°	9	33	52

Alkylation by new method.

This new method consists of combining the alkylation with diethyl carbonate condensation.



Phenylacetonitrile — Diethyl carbonate — Ethyl cyanophenylacetate, sodium salt



Ethyl cyanophenylacetate, sodium salt — Alkyl halide — Ethyl alkylcyanophenylacetate

__Reactants in grams__

Alkylating agent	Benzyl cyanide	Diethyl carbonate	Sodamide	Halide	Ether
Isopropyl bromide,	45	60	16	50	200
Tertiaryamyl iodide,	25	35	10	35	200

The pulverized sodamide was added to the ether, and then the phenylacetonitrile was added dropwise. After refluxing for about a half hour the diethyl carbonate was introduced drop by drop, and the

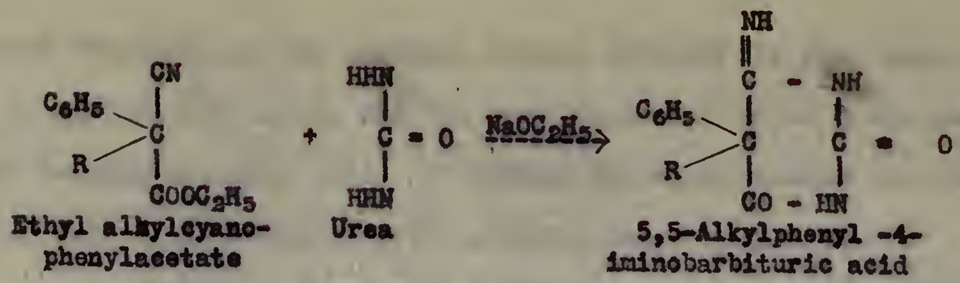
reaction mixture was refluxed for about two hours. At this time such a large quantity of the solid sodium salt of ethyl cyanophenylacetate had formed that only the center portion was being stirred. However, by increasing the speed of the stirrer, the whole mass gradually became agitated once more. The alkyl halide was then slowly added and the reaction mixture refluxed for four days. Enough water was added to dissolve the sodium halide, and the aqueous layer was acidified with dilute sulphuric acid (20% by weight). The ether layer and ether extracts of the water layer were dried over calcium chloride and distilled under reduced pressure. The results of the two attempted alkylations are as follows:

	b.p.	press. in mm.	g.	mol. wt. (f.p.)
Isopropyl,	150-160°	10	30.6	190
Tertiaryamyl (a)	150-160°	12	12.5	190
(b)	155-165°	12	7.0	
Ethyl cyanophenyl-acetate,	140-160°	13	-	189

From the above boiling point and molecular weight determinations, it is evident that no alkylation was effected as the product was simply ethyl cyanophenylacetate.

III. Urea Condensation.

The condensation of ethyl alkylcyanophenylacetate with urea resulted in the 5,5-alkylphenyl-4-iminobarbituric acid. The procedure of Conrad[10] (with several modifications) was followed.



The first urea condensation to be carried out in this investigation was with the heptyl ester. As will be shown later several modifications of this procedure were made in the condensation of urea with the isopropyl and the tertiaryamyl esters.

Sodium ethylate was prepared from 100 g. of absolute ethyl alcohol and 6.5 g. of sodium chips. Approximately one-half (16 g.) of the ethyl cyanoheptylphenylacetate was added slowly, immediately followed by 10 g. of urea. Due to the sudden appearance of a purple color, the remainder of the ester, 33 g. in all, was hastily added. After refluxing for eight hours the alcohol was distilled off. The residue was dissolved in water (about 600 cc.) and the unchanged ester was removed by extraction with ether. Upon acidifying the aqueous layer with concentrated hydrochloric acid a white crystalline precipitate, 5,5-hdptylphenyl-4-iminobarbituric acid settled out. This was recrystallized from 95% alcohol. Yield, 2 g. = 5%, m.p. 252°C.

Since the yield of iminobarbituric acid was so low, several variations were made in carrying out the reaction.

As explained on page 14, it was thought that conditions for condensation might be made more favorable by forming the sodium salt of the alkylated ester and then adding urea to this sodium salt.

Sodium ethylate was made from 50 g. of absolute ethyl alcohol and 1 g. of sodium. Five grams of ethyl cyanoisopropylphenylacetate were

added dropwise, and the reaction mixture refluxed for five hours. Then 2 g. of urea were added, and the reaction carried on as in the case of the heptylphenylimino acid. Acidifying the water resulted in a turbidity only, not in a flocculent white precipitate.

In the two cases just referred to, the urea was added as a dry powder. An attempt was made to secure condensation by introducing the urea as a solution.

Sodium ethylate was made from 100 g. of alcohol and 5 g. of sodium chips. Six grams of urea were dissolved in about 100 g. of hot absolute alcohol and the ester was added to this solution. After the solution had been added slowly to the sodium alcoholate, the procedure was the same as in the first instance cited. Again, only a cloudiness appeared instead of a white precipitate.

The next modification of procedure in the condensation of the alkylated ester with urea was to use an excess of urea.

Two grams of sodium were added to 50 cc. of absolute alcohol. This was followed by 2.3 g. (theoretical amount) of urea, and then 7 g. of the isopropyl ester. After refluxing overnight, 2 g. more of urea were added. As before, no iminobarbituric acid was obtained.

It was thought possible that a refluxing period of ten hours was not sufficient, so in the next trial the urea and ester were refluxed about thirty-six hours.

Three grams of dry urea were added to sodium ethylate made from 50 cc. of absolute alcohol and 2 g. of sodium chips. Ten grams of the isopropyl ester were added, and the reaction mixture was refluxed for two days and a night. No well defined precipitate but merely a turbidity appeared upon acidifying the aqueous layer.

Finally, as in the case of the heptylphenylimino barbituric acid, part of the isopropylester was first added to the sodium ethylate, then the urea, and finally the rest of the ester.

To 100 g. of absolute alcohol were added 4 g. of chipped sodium. To this sodium ethylate 7 g. of ethyl cyanoisopropylphenylacetate, 6 g. of urea, and then 7 g. more of ethyl cyanoisopropylphenylacetate were successively introduced. Again, no iminobarbituric acid was obtained.

The preparation of tertiaryamylphenyliminobarbituric acid was attempted by introducing into sodium ethylate, made from 200 g. of absolute alcohol and 2 g. of sodium, 5 g. of dry urea immediately followed by 10 g. of the tertiaryamyl ester. No tertiaryamylphenyliminobarbituric acid was produced by this procedure.

The variations made in the urea condensation are as follows:

I. The ester was refluxed in the sodium ethylate for several hours before the urea was added.

II. The urea was added as a solution instead of dry.

III. A large excess over the theoretical amount of urea was used.

IV. The period of refluxing the urea and ester together in the sodium alcoholate was increased.

In all cases, the modifications of the procedure gave only negative results so far as the condensation was concerned.

Heptylphenylbarbituric acid

The preparation of only one of the final barbituric acids was carried through to completion, viz., that of the heptylphenylbarbituric acid. In this case the heptylphenyliminobarbituric acid described on page 19 was hydrolyzed with hydrochloric acid.

One and one-half grams of the imino acid were put into 100 cc. of hydrochloric acid of specific gravity 1.05. The mixture was refluxed about two hours. The white crystalline substance was filtered off and recrystallized from 95% alcohol. The recrystallized heptylphenylbarbituric acid was a beautiful white glistening compound, m.p. 150°, yield, 1.0 g. = 63%.

SUMMARY

The work done in the present investigation may be summed up in the following form:

(A) The study of the preparation, by methods used by other workers in this laboratory and as cited in previous references, of

(1) 5,5-Isopropylphenylbarbituric acid (not obtained) with the intermediate

(a) Ethyl cyanophenylacetate.
(b) Ethyl cyanoisopropylphenylacetate.
(c) 5,5-Isopropylphenyl-4-iminobarbituric acid.

(2) 5,5-Heptylphenylbarbituric acid with the intermediate

(a) Same as (1).
(b) Ethyl cyanoheptylphenylacetate.
(c) 5,5-Heptylphenyl-4-iminobarbituric acid.

(3) 5,5-Tertiaryamylphenylbarbituric acid (not obtained)

(a) Same as in (1)
(b) Ethyl cyanotertiaryamylphenylacetate.
(c) 5,5-Tertiaryamylphenyl-4-iminobarbituric acid.

(B) The study of certain modifications of the procedure in effecting these preparations.

(1) The combining of two steps, - diethyl carbonate condensation and alkylation.

(2) In the urea condensation, the use of

(a) A longer refluxing period of the ester and sodium ethylate before the addition of any urea.
(b) An alcoholic solution of urea.
(c) A longer refluxing period of the alkylated ester and urea.
(d) An excess of urea.

Although thoroughly tried, in some cases several times, none of these modifications improved the yield, and in most instances gave no resulting product whatever.

CONCLUSIONS

The conclusion, therefore, is very brief, viz., that no modification of the procedure previously adopted in this laboratory for this synthesis of 5,5-Alkylphenylbarbituric acids, has been found as a result of this investigation.

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Approved:

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Graduate Committee.

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